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The Liquisolid Technique: Based Drug Delivery System

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ABSTRACT
The "Liquisolid" technique is a novel and capable addition towards such an aims for solubility enhancement and dissolution improvement, thereby it increases the bioavailability. It contains liquid medications in powdered form. This technique is an efficient method for formulating water insoluble and water soluble drugs. This technique is based upon the admixture of drug loaded solutions with appropriate carrier and coating materials. The use of non-volatile solvent causes improved wettability and ensures molecular dispersion of drug in the formulation and leads to enhance solubility. By using hydrophobic carriers (non-volatile solvents) one can modify release (sustained release) of drugs by this technique. Liquisolid system is characterized by flow behavior, wettability, powder bed hydrophilicity, saturation solubility, drug content, differential scanning calorimetry, Fourier transform infra red spectroscopy, powder X-ray diffraction, scanning electron microscopy, *in-vitro* release and *in-vivo* evaluation. By using this technique, solubility and dissolution rate can be improved, sustained drug delivery systems be developed for the water soluble drugs.

Keywords: Liquisolids, carriers, coating materials, water in-soluble/ soluble drugs.

INTRODUCTION

The liquisolid technique as described by Spireas [1] is a novel concept, where a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material. [1-2] The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is included into the porous carrier material. Inert, preferably water-miscible organic solvent systems with high boiling point such as liquid polyethylene glycols, propylene glycol, or glycerine are most excellent fitting as liquid vehicles. As the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. [3-4] The liquisolid compacts are acceptably flowing and compressible powdered forms of liquid medications. The term '*liquid medication*' refers to liquid lipophilic (oily) drugs or water-insoluble solid drugs dissolved in suitable water-miscible non-volatile solvent systems termed as the liquid vehicle. [5] Such liquid medication may be converted into a dry-looking, non-adherent, free flowing and readily compressible powders by a simple admixture with selected powder excipients referred to as the "carrier and coating materials". In the liquisolid systems, even though the drug might be in a solid dosage form, it is held within the powder substrate in solution or in a solubilized, almost molecularly dispersed state. [6] Therefore, due to their significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release characteristics and consequently improved oral bioavailability. [6-7] In current generation inadequate solubility of drugs, which are demanding issue for industry throughout development of the ideal solid dosage unit This technique is based upon the admixture of drug loaded solutions or liquid drug with appropriate carrier and coating materials. [8] Addition of the additives improves the technique. The selection of non-toxic hydrophilic solvent, carrier, coating excipients and its ratios are independent of the individual chemical entities and it leads to enhance the solubility and bioavailability. [7-9] However, poorly soluble drugs with low dose chemical entities are more ideal to formulate in the above said technique. [10] The powdered form of the liquid medications shows rapid disintegration rates are noticed compared to conventional tablets, showed improved release rates and better bioavailability. The different methods to enhance the solubility are shown in Fig. 1. The use of non-volatile solvent causes increased wettability and ensures molecular dispersion of drug in the formulation and by using hydrophobic polymers and excipients carriers such as Eudragit RL and Eudragit RS controlled release of drugs from the liquisolid tablets as the dosage forms can be formulated. [1] This paper

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focuses on the novel technique and shows potential technology of liquisolid compact effects on dissolution and bioavailability. From the historical point of view, liquisolid compacts were evolved from 'Powdered Solutions' which depended on preparing a homogenous solution of the drug in a high boiling point, water-miscible solvent, which was carried out on the extensive surface of an inert carrier such as silica. [11] It is possible to produce at low cost and ability to produce industrially. Liquisolid system refers to formulations formed by conversion of drugs into liquid forms, as suspensions or solution in nonvolatile solvents into dry, free-flowing, non-adherent, and compressible powder mixtures by combining the suspension or solution with selected carriers and coating materials. [12-14] Due to significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble substances expected to displayed enhanced drug release characteristics and, consequently improved oral bioavailability. [15-16] Since dissolution of a lipophilic drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution, thereby displaying improved dissolution rates. [17] That is why soft gelatin capsules containing solutions of such medications demonstrate higher bioavailability whilst to that of conventional oral solid dosage forms. [18] A similar principle underlies the mechanism of drug delivery from liquisolid compacts and is chiefly responsible for the improved dissolution rates exhibited by these arrangements as shown in the Fig. 2. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution or in a solubilized, almost molecularly dispersed state, which contributes to the improved drug dissolution properties. [19]

ADVANTAGES

1) Huge number of Bio-Pharmaceutical classification class II drugs with high permeability, slightly or very slightly water soluble and practically insoluble liquids and solid drugs can be formulated into liquisolid systems.
2) Improvement of bioavailability of an orally administered water insoluble drugs is achieved.
3) This principle governs or administers the mechanism of drug delivery from liquisolid systems of powdered drug solutions and it is mainly responsible for the improved dissolution profiles exhibited by this preparations.
4) In this technique, production cost is low compared to soft gelatin capsules.
5) Drug is formulated in a tablet form or encapsulated dosage form and is held in solubilized liquid state, which confers developed or improved drug wetting properties thereby improving drug dissolution profiles.
6) Greater drug surface area is exposed to the dissolution medium.
7) This liquisolid system is specifically for powdered liquid medications.
8) These liquisolid systems formulate into immediate release or sustained release dosage forms.
9) Optimized sustained release, liquisolid tablets or capsules of water insoluble drugs demonstrate constant dissolution rates (zero order release).
10) It is used in controlled drug delivery systems.
11) Drug can be molecularly dispersed in the formulation.
12) Drug release can be modified using suitable formulation ingredients.
13) Capability of industrial production is also possible.
14) Enhanced bioavailability can be obtained as compared to conventional tablets.
15) Differentiate the dosage form by admixture of colour into liquid vehicle.
16) To minimize excipients in formulation compare with other formulations like solid dispersions.
17) Omit the process approaches like nanonisation, micronization techniques.

DISADVANTAGES

1) Formulation of high dose lipophilic drugs the liquisolid tablet is one of the limitations of this technique.
2) In order to achieve acceptable flowability and compactability for liquisolid powder formulation, high levels of carrier material and coating materials should be added. This will increase the weight of tablets to above one gram which makes them difficult to swallow. Consequently, it is impossible with conventional tablet methods to convert high dose to liquisolid tablets with a tablet weight of less than 50mg. Dissolution profile enhancement occurs in the presence of low levels of hydrophilic carrier, where coating material is not significant.

The most important formulation components of liquisolid technique are [19-23, 25]

Liquid medication: Lipophilic drugs and drug suspensions or solutions of solid water–insoluble drugs in suitable non volatile solvent systems are called Liquid medication.

Solubility: The amount of drug that passes into solution in order to establish the equilibrium at constant temperature and pressure and so produce a saturate solution is known as the solubility of the substance**,** water insoluble drugs include those drugs that are "sparingly water soluble" (1 part solute into 30-100 parts of H_2O), slightly water- insoluble (1 part solute into 1000 -10,000 parts of H_2O) and practically "water-insoluble" or insoluble (1 part solute into 10,000 or more parts of H_2O).

Spectroscopic method: This is carried out by preparing saturated solutions of drug in non volatile solutions and analyzing them spectrophotometrically. These saturated solutions are prepared by adding drug to the solvent and placed in orbital shaker for 25°C for specific time period under constant vibration. Then the solutions are filtered and analyzed spectrophotometrically.

Liquisolid technique: It refers to powdered forms of liquid medications formulated by changing to liquid lipophilic drugs or solutions or drug suspensions of water insoluble solid drugs in suitable non-volatile solvent systems into dry-looking, non-adherent, free flowing.

Type of Liquisolid compacts based on the liquid medication, it divided into three sub groups:

1. Powdered drug solutions
2. Powdered drug suspensions
3. Powdered liquid drug

The first two groups may exist or be produced by changing drug solutions and drug suspensions while the third is produced from the formulation of liquid drugs into liquisolid systems.

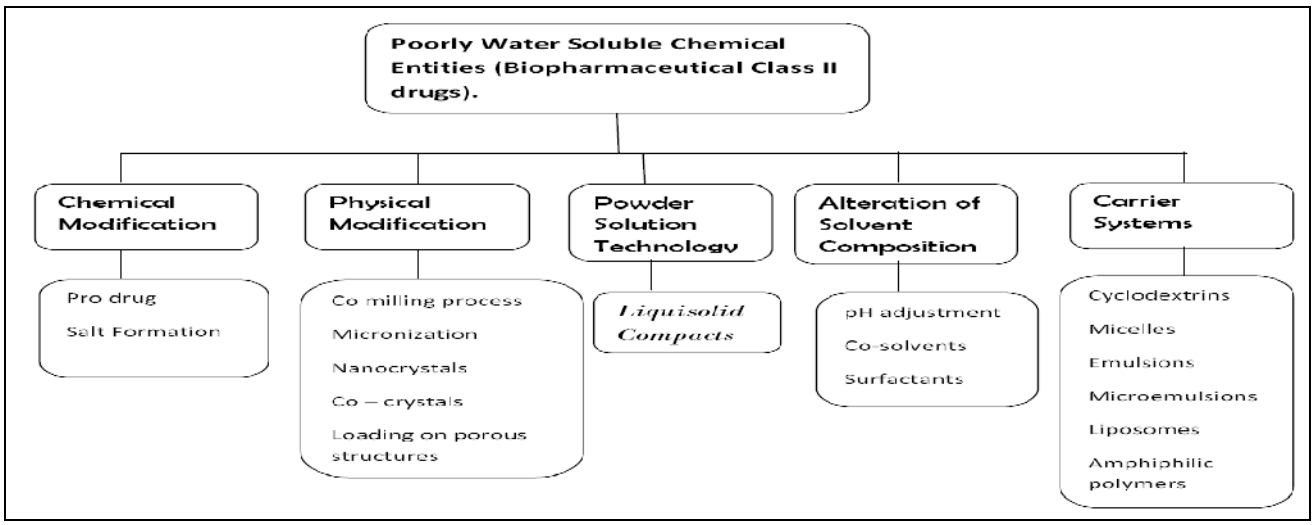

Fig. 1: Different methods to enhance the solubility of drugs

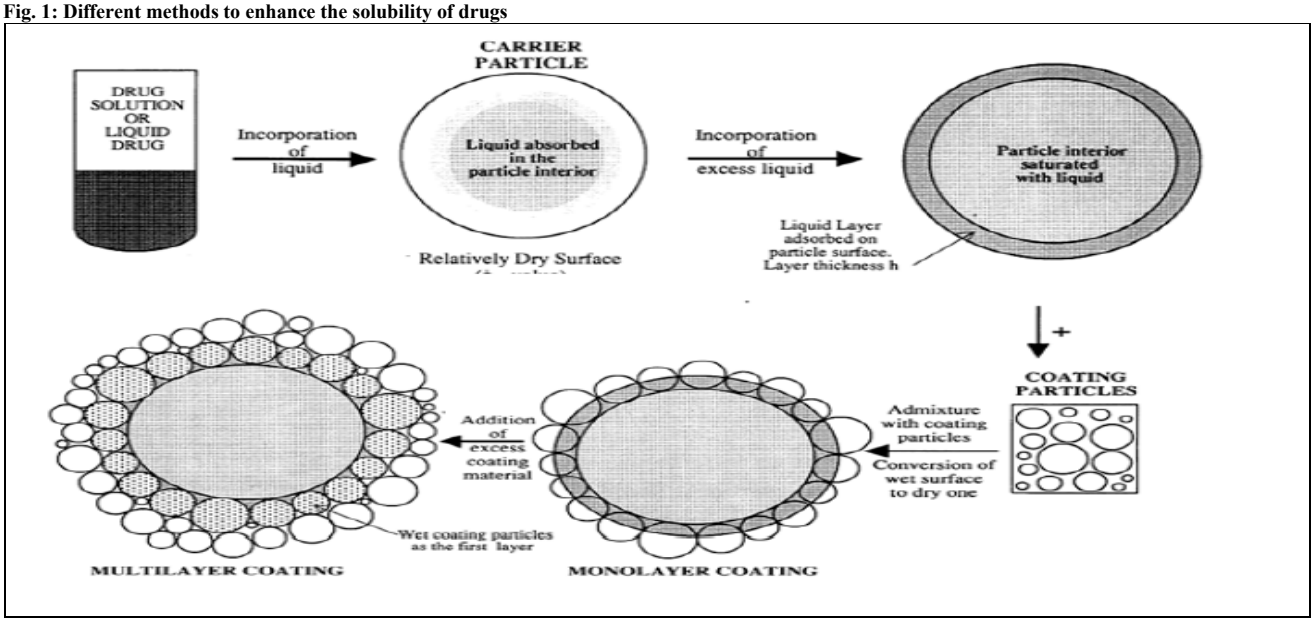

Fig. 2: Mechanism represents formulation of liquisolid system

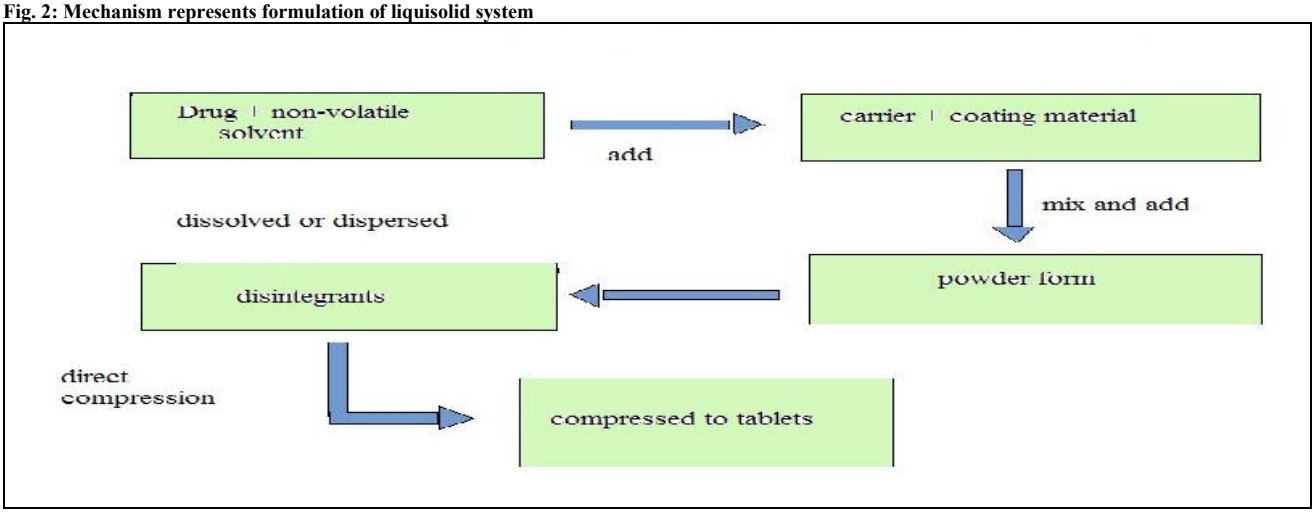

Fig. 3: Method of Preparation of Liquisolid Tablets

Liquisolid compacts: It refers to immediate sustained-release tablets or capsules that are described under liquisolid systems.

Liquisolid microsystems: It refers to capsules prepared by liquisolid systems with the inclusion of an additive ensuing in a unit size that may be as much as five times less than that of a liquisolid compact.

Carrier: Coating Material Ratio (R): It is the ratio between the quantities of carrier (Q) and coating materials (q) present in the formulation. It is represented as:

$$R = \frac{Q}{q}$$

Coating Material: It is a substance possessing fine and highly adsorptive particles. These are flow-enhancing, very fine 10 nm to 5,000 nm in diameter, highly adsorptive coating particles

e. g: silica of various grades like Cab-O-Sil M5, Aerosil 200, Syloid244FP etc., contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid.[23, 26-28]

Carrier material: These are as porous substance possessing adequate absorption properties. Various grades of microcrystalline cellulose (MCC) such as pH101, and 200 Avicel® RTM 105, Avicel® pH 102 granular Microcrystalline cellulose (MCC) grade, Avicel ® pH 200 coarse granular MCC grade, experimental grade of granular amorphous cellulose, starch, lactose used as carrier materials. Starch 1500, Silica possessing large surface areas and MCC of fine particle size granular grades produced good flow properties and compression properties resulting in good tablets.

Hydrophobic carrier: Eudragit RL and RS [28], HPMC K4M [29] etc, for sustained release.

Liquid load factor (Lf): It is the ratio of the amount of liquid medication (W) over the quantity of carrier material (Q) in the system. The ratio can be calculated with this equation:

$$L_f = \frac{W}{Q}$$

Super disintegrants: Sodium starch glycolate [30] Explotab13, Pumogel, Crosspovidone, [31] Sodium croscarmellose, [32-33] Pre gelatinized starch. [34]

Non-Volatile solvents: preferably water-miscible, Inert high boiling point and not highly viscous organic solvent systems e.g. propylene glycol, liquid polyethylene glycols, N, N dimethylacetamide, polysorbates, glycerin, fixed oils etc., are most suitable as vehicles. [35]

Designing of Liquisolid Systems

Before designing the liquisolid, the Preformulation studies should be performed first, these include

1. Determination of drug in different non-volatile solvents
2. Determination of angle of slide
3. Determination of flowable liquid retention potential (Ø value)
4. Calculation of liquid load factor (L_f)
5. Liquid solid compressability test (LSC)

The flowability and compressibility of liquisolid compacts are addressed concurrently in the new formulation mathematical model of liquisolid systems, which was used to calculate the appropriate quantities of the carrier and coating materials required to produce acceptably flowing and compressible powders based on new fundamental powder properties called the flowable liquid retention potential (Φ - value) and compressible liquid retention potential (Ψ - number) of the constituent powders. [37-38]

Determination of drug in different non-volatile solvents: These are carried by preparing saturated solutions of drug in non-volatile solvents, and analyzing them spectophotometrically. [39] Saturated solutions are prepared by adding excess of drug to vehicles and shaking them on shaker for specific time period under steady vibration. After this, the solutions are filtered and analyzed spectrophotometrically.

Determination of angle of slide: The required amount of carrier is weighed and placed at one of a metal plate with a polished surface and it is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide. [40] It was used to measure the flow properties of powders. The angle of 33° is optimum for flow of powders.

Determination of liquid flowable liquid retention potential (Φ): –It is defined as the maximum weight of liquid that can be retained per unit powder material in order to produce and acceptably flowing liquid/powder admixture. This Φ –value of powders may be determined using a new procedure, the liquisolid flowability (LSF) test. The Ø value was used to calculate excipients quantities. Equation for this is as follows:

$$L_f = \boldsymbol{Ø} + Ø\,(1 / R)$$

Where **Ø** and Ø are the constant Ø values of carrier and coating materials, respectively. By calculating L_f and W, we can calculate the amount of Q and q required for liquisolid systems. [19]

Calculation of liquid load factor (L_f)

It is defined as the ratio of weight of liquid medication (w) to weight of carrier material (Q). Differnt concentrations of nonvolatile solvents are taken and the drug is dissolved and the carrier coating material is added and blended. [41]

$$L_f = W/Q$$

W=ratio of weight of liquid medication

Q= weight of carrier material

The liquid load factor that ensures acceptable flowability (L_f), and can be measured by:

$$L_f = (1/R)$$

Liquisolid compressability test (LSC)

It was developed to determine Ψ values and involves steps such as preparing carrier coating material admixture systems,[42] preparing several uniform liquid/powder admixtures to tablets, determining average hardness, measuring of average liquid content of crushed tablets, as well as determining plasticity, sponge index and Ψ value and L_f.

General Procedure for Liquisolid Tablets

The liquisolid tablet preparation method involves, first a mathematically calculated amount of pure drug weighed and dissolved in the suitable amount of solvent in a molecularly dispersed state. For attaining good flow properties trial and error methods were used i.e. changing the carrier: coating material ratio from 50:1 to 5:1 ratios according to new mathematical model expressions proposed by Liao. [43] This liquid medication is poured on the suitable amount of carrier material. The liquid medication is absorbed into the carrier material internally and externally and then a suitable disintegrant was added to this material. Finally, coating material was added for dry looking, adherent to the carrier material for achieving good compression properties. Liquid medication is incorporated into carrier material which has a porous surface and closely matted fibers in its interior as cellulose. [44] Both absorption and adsorption take place, i.e. the liquid absorbed into the interior of the particles is captured by its internal structure and after saturation of this process, adsorption of the liquid onto the internal and external surface of the porous carrier particles occurs. [43] Excipients possessing fine and highly adsorptive particles such as various types of amorphous silicon dioxide (silica)

are most suitable for this step. Before compression or encapsulation, various ingredients such as lubricants disintegrants or Polymers, and binders (as shown in Fig. 3), may be mixed with the finished liquisolid systems to produce liquisolid compacts in the dosage form of tablets or capsules. [45-47]

Evaluation of liquisolid systems

Flow behavior

The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to reduce high dose variations. [48] Angle of repose, Carr's index and Hausner's ratio were used in order to ensure the flow properties of the liquisolid systems. [49]

Pre compression studies of the prepared liquisolid

Powder systems: In order to ensure the suitability of the selected excipients, Fourier Transform Infra Red Spectroscopy, Differential scanning Calorimetry, X-ray Diffraction and Scanning Electron Microscope studies are to be performed. In addition, flowability studies are also to be carried out to select the optimal formulae for compression, prior to the compression of the powders the dosage forms such as into tablets and capsules.

Fourier Transform Infra Red Spectroscopy (FT-IR)

FT-IR spectra of prepared melt granules are recorded on FTIR-8400 spectrophotometer. Potassium bromide (KBr) pellet method is employed and background spectrum is collected under identical situation. Each spectrum is derived from single average scans collected in the region 400 - 4000cm^{-1} at spectral resolution of 2cm^{-2} and ratio against background interfereogram. Spectra are analyzed by software. [37]

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) is performed in order to assess the thermotropic properties and the thermal behaviors of the drug, excipients used in the formulation of the liquisolid system. Complete disappearance of characteristic peaks of drug indicates the formation of drug solution in the liquisolid powdered system, i.e., the drug is molecularly dispersed within the liquisolid matrix. [50-51, 37]

X-ray diffraction (XRD)

For the characterization of crystalline state, X-ray diffraction (XRD) patterns are determined for physical mixture of drug and excipients used in formulation and for the prepared liquisolid compacts. [53] Absence of constructive specific peaks of the drug in the liquisolid compacts in X-ray diffractogram specify that drug has almost entirely converted from crystalline to amorphous or solubilized form. Such lack of crystallinity in the liquisolid system was understood to be as a result of drug solubilization in the liquid vehicle i.e., the drug has formed a solid solution within the carrier matrix. This amorphization or solubilization of drug in the liquisolid compacts it may contribute to the consequent improvement in the apparent solubility and enhancement of dissolution rate of the drug. [8]

Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) is utilized to assess the morphological characteristics of the raw materials and the drug-carrier systems. [8]

Contact angle measurement

For assessment of wettability, contact angle of liquisolid tablets is measured according to the imaging method. The commonly used method is to measure contact angle directly for a drop of liquid resting on a plane surface of the solid, the so-called imaging method. A saturated solution of the drug in dissolution media is prepared and a drop of this solution is put on the surface of tablets. The contact angles are calculated by measuring the height and diameter of sphere drop on the tablet. [53]

***In vitro* dissolution studies**

Works of many researchers revealed that technique of liquisolid compacts could be a promising alternative for formulation of water-insoluble drugs. This technique of liquisolid compacts has been successfully employed to improve the *in-vitro* release of poorly water soluble drugs as hydrocortisone, [23] Prednisolone [19] Carbamazepine [51] Piroxicam. [28, 52-53] Also several water insoluble drugs nifedipine, gemfibrozil, and ibuprofen, have shown higher bioavailability in rats as compared to their commercial counterparts.

***In vivo evaluation* of liquisolid systems**

This liquisolid technology is a promising tool for the enhancement of drug release of poorly soluble drugs. The absorption characteristics of Hydroclorothiazide liquisolid compacts in comparison with commercial tablets were studied in beagle dogs. Significant differences in the area under the plasma concentration-time curve, the peak plasma concentration and the absolute bioavailability of the liquisolid and the commercial tablets were observed. However, for the mean residence time, the mean absorption time, and the rate of absorption no significant differences were found. The absolute bioavailability of the drug from liquisolid compacts was 15% higher than that from the commercial formulation. [7]

Brief Indication of Existing Formulations to Produce Liquisolid Compact

Liquisolid Compact as Sustained Release of Drug from its Dosage Unit

Development of sustained release oral dosage forms is beneficial for optimal therapy in terms of efficacy, safety and patient compliance. Superlatively, a controlled release dosage form will provide therapeutic concentration of the drug in the blood, and it is maintained throughout the dosing interval. To achieve this intend; numerous methods have been developed such as preparation of salt form of drug, coating with special materials and incorporation of drugs into hydrophobic carriers. Liquisolid technique is a new and promising method that can change the dissolution rate of drugs. [29]

Tramadol hydrochloride (TH) liquisolid compact formulated to evaluate sustained release dosage form. The dissolution profile of the prepared compacts was also compared to that of a marketed formulation. Liquisolid sustained release formulations were prepared by using HPMC K4M as a release retarding agent. Liquisolid compacts were evaluated by friability, hardness and *in vitro* dissolution studies. Comparison of dissolution profiles was carried out by using a model independent, model-dependent and statistical approach. The liquisolid dosage forms shows better sustained release behavior compared to a marketed sustained formulation. The dissolution profile followed the Peppas model as best fit model. Two-way ANOVA results revealed a significant difference in dissolution profiles. This systematic approach to producing a formulation was found to help with analyzing the sustained release of TH. These methods provide an acceptable model approach that indicates the true association between percent drug release and time variables, including statistical assumptions. [29]

Propranolol hydrochloride (PHCL) is a β - adrenergic blocking agent, i.e. a competitive inhibitor of the effects of catecholamines at β - adrenergic receptor sites. It is widely used in therapeutics for its antihypertensive and antiarrhythmic properties. Furthermore, it has a short elimination half-life of 3h, which makes it a suitable candidate to be delivered at a controlled rate. [54]

It is suggested that liquisolid technique has the potential to be optimized for the reduction of drug dissolution rate and there by production of sustained release systems. In this study, PHCL was dispersed in polysorbate 80 as the liquid vehicle. The selection is based on the least solubility of liquid vehicle. Then a binary mixture of carrier - coating materials (Eudragit RS or Eudragit RL as the carrier and silica as the coating material) was added to the liquid medication under constant mixing in a mortar. The effect of drug concentration, thermal treating, loading factor and aging on release profile of PHCL from liquisolid compacts were investigated at pH 1.2 and pH 6.8. Tablets prepared by liquisolid technique showed higher retardation properties in evaluation with conventional matrix tablets. The results also revealed that wet granulation had remarkable impact on release rate of PHCL from liquisolid compacts, decreasing the release rate of PHCL from liquisolid compacts. The kinetics data revealed that most of the liquisolid formulations followed the zero-order release pattern. [17]

Approach to Enhance Dissolution of Drug Release from its Immediate Release Tablets

In the liquisolid systems the drug might be in a solid form, it is held within the powder substrate in solution, or in a solubilized, almost molecularly dispersed state, consequently, due to their significantly increased wetting properties and surface of drug available for dissolution. Liquisolid compacts of water- insoluble substances may be expected to display enhanced drug release properties and simultaneously improved bioavailability. [20]

Rofecoxib is a practically insoluble nonsteroidal anti-inflammatory drug. The liquisolid tablets of Rofecoxib showed significant increased in dissolution profiles compared to the commercial tablets. [56, 61]

Naproxen is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the reduction of fever, pain and inflammation. Liquisolid compacts change the properties of naproxen particles by simply dispersing the drug particles in a non-volatile hydrophilic liquid vehicle, which increase the wetting properties of drug particles, and enhances the dissolution rate and shows improved bioavailability of the drug. At present, naproxen is available commercially in high dose tablets between 250 and 500 mg; the liquisolid formulations may help in reduction of the dose also. [56]

Bromhexine hydrochloride (BXH) is a mucolytic agent used in the treatment of respiratory disorders associated with viscid or excessive mucus. It has a poor solubility which is a major factor in the design of pharmaceutical formulations. Liquisolid compacts of BXH were distinctly higher compared to directly compressed tablets. It shows significant advantages of liquisolid in increasing wetting properties and surface area of drug available for dissolution. [57]

Prednisolone, a very slightly water soluble glucocorticoid, prepared in directly compressed tablets and liquisolid compacts. According to the prepared method of liquisolid compacts, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile liquid vehicles can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. It has been speculated that such systems shows enhanced release profiles owing to the increased wetting properties and surface of drug obtainable for dissolution. Several liquisolid tablet formulations were prepared by applying a new mathematical model to calculate the appropriate quantities of powder and liquid ingredients required to produce acceptably flowing and compressible admixtures.

Liquisolid compacts confirmed significantly higher drug release rates, in different dissolution media, compared to tablets prepared by the direct compression method. It was also observed that the drug dissolution rate from liquisolid tablets were independent of the volume of dissolution medium, in difference to the plain tablets which expose declining drug release patterns with decreasing dissolution volumes. [19]

Piroxicam (PX) is a class II drug according to BCS as it possesses poor water solubility and highly permeability. The rate of its oral absorption is often controlled by the dissolution rate in the gastrointestinal. The poor dissolution rate of water insoluble drugs is still a major problem confronting the pharmaceutical industry. There are several techniques to enhance the dissolution of poorly soluble drugs. Among them, the technique of liquisolid compacts is a promising technique towards such a novel aim. In this study, the dissolution behavior of PX from liquisolid compacts was investigated in simulated gastric fluid (SGF, pH1.2) and simulated intestinal fluid (SIF, pH 7.2). Several liquisolid tablets formulations containing various ratios of drug: Tween 80 (10% to 50% w/w) was prepared. The ratio of MCC as a carrier to silica as coating powder material was kept constant in all formulations. The results showed that liquisolid compacts demonstrated considerably higher drug release rates than those of conventionally made capsules and directly compressed tablets containing micronized PX. The higher dissolution rates displayed by liquisolid compacts may also imply enhanced oral bioavailability due to the increased wetting properties and surface of drug available for dissolution. This study reveals that, the liquisolid compacts of PX in which polysorbate 80 is the liquid vehicle, in different drug concentrations in their liquid medications, exhibit drug dissolution rates which are directly proportional to the fraction of the molecularly dispersed drug in their liquid medication. [4, 51] It is concluded that liquisolid compacts technique can be a promising alternative for the formulation of water-insoluble drugs.

Carbamazepine (CBZ), 5H-dibenzazepine-5-carboxamide, is a sodium channelblocker that has been in routine use in the treatment of epilepsy and trigeminal neuralgia for over 40 years. CBZ is considered a first line drug in the treatment of Epilepsy. It is practically insoluble in water. The oral absorption of CBZ is slow, erratic and unpredictable in humans owing to slow dissolution. Many studies were done in trial to improve the bioavailability of CBZ. This drug also belongs to class II, that its bioavailability is limited by its poor dissolution rate in GI. In fact, its solubility and dissolution rate are key factors in its bioavailability. Different liquisolid formulations of CBZ were consummate by dissolving the drug in the non-toxic hydrophilic liquids, and adsorbing the solution onto the surface of silica. To reduce the amounts of carrier and aerosil in liquisolid formulations,

some namely additives Polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC) and polyethylene glycol (PEG 35000) were added to liquid medication to increase loading factor. The effects of various ratios of carrier to coating material, effect the aging and type of the carrier on dissolution rate of liquisolid compacts were studied. [16, 57-58]

Cyclosporine (CS) Self Micro-Emulsifying Tablet (SME), the tablets were prepared by the liquisolid compaction technique. Formulation consists of oil, surfactant and co-surfactant which were selected on the basis of solubility and emulsification ability for the SME formulation. In this study, the mixture of Lauroglycol FCC: Maisine 35-1 (1: 1w/w) was selected as the oil phase, PEG-35 Castor Oil was selected as the surfactant and PEG-400 was selected as the co-surfactant. 1 to 6 was selected as the ratio between the drug and the mixture. An Emulsion could not be formed in several oils, such as Carpryol 90, Lauroglyol 90 and Lauroglycol FCC even in which the CS has good solubility. Due to the cyclic structure of CS-A, some excipients absorbed the drug and could not be selected as carrier material and coating material, e.g., silica powders. The liquisolid tablets were effective in enhancing dissolution of CS-A, a poorly water-soluble drug. The tablets exhibited good flowability and compactability. The results showed that the liquisolid compaction technique is a promising alternative technique to improve the solubility and the dissolution rate, for poorly water-soluble drugs CS-A. [59]

Estimation of Bioavailability

Bioavailability assessment is required for liquisolid technique. Because it was proved that enhancing the drug releases from the dosage form by determination of *in-vitro* release studies. So, this parameter should establish for determination of the efficacy of the formulation. [4]

Atorvastatin calcium (ATR) is a BCS class II drug used as a lipid lowering agent by acting as HMGCoA reductase inhibitor. The prepared liquisolid compacts of ATR showed higher release rates compared to the directly compressed tablets. The pharmacokinetic parameters of liquisolid compacts of ATR, such as the AUC, t_{max} and C_{max} showed the better bioavailability compared with the conventional formulation. [60]

Famotidine (FM) is indicated for active and maintenance therapy of various types of ulcers and hyper secretory conditions. The mechanism of action, pharmacological effects, site of action, and clinical uses are the same as for the other H_2-receptor antagonists, but on equimolar bases. FM is reported to be about 7.5 and 20 times more potent than ranitidine and cimetidine respectively, in inhibiting gastric acid secretion. However, FM is relatively free of side effects despite its high potency. Although FM reportedly undergoes minimal first pass metabolism and its oral bioavailability in man has been reported to be low and variable, ranging from 40% to 50% due to its poor aqueous solubility, high polarity, and gastric degradation. Since for poorly water-soluble drugs (like FM) the dissolution rate is often the rate limiting step for bioavailability, and the dissolution rate is a purpose of the solubility and the surface area of the drug available, thus, dissolution rate will increase if the solubility of the drug is increased, and dissolution rate be enhanced with an increase in the surface area of the drug. [20]

This study was to improve FM dissolution through its formulation into liquisolid systems and then to investigate the *in-vitro* and i*n- vivo* performance of the formulated liquisolid tablets. All the formulations showed higher drug dissolution rates than the conventional and directly compressed tablets. Selected optimal formula released 78.36% of its content during the first 10 min, which is 39% higher than that of the directly compressed tablets. The bioavailability study indicated that the prepared optimal liquisolid formula did not differ significantly from the marketed FM tablets relating to C_{max}, t_{max}, and $AUC_{(0–8)}$ at $P < 0.05$ by statistical analysis (ANOVA).[20]

Repaglinide (RP) is a novel post prandial glucose regulator for the treatment of type 2 diabetes mellitus. It helps to control blood sugar by stimulating release of insulin from the pancreatic β- cells. Repaglinide is rapidly absorbed from the gastrointestinal tract after oral administration. In this study it was designed to determine the bioavailability and biological activity of liquisolid compact formula of repaglinide and its effect on glucose tolerance in rabbits. This study is an extension of the previous enhancement of dissolution properties of repaglinide using liquisolid compacts. The development and validation of a High Performance Liquid Chromatography (HPLC) assay for the determination of repaglinide concentration in rabbit plasma for pharmacokinetic studies is described. Repaglinide optimizing formula was orally administered to rabbits and blood samples were used to determine the pharmacokinetic parameters of repaglinide, which were compared to pharmacokinetic parameters of marketed tablets (Novonorm 2 mg). To investigate the biological activity of this new formula, in comparison with the commercial product, Oral Glucose Tolerance Tests (OGTT), area under the curve and insulin levels were studied. Moreover, we studied the efficacy and safety of this new formula in several potencies i.e 0.5, 1, and 2 mg and blood glucose, insulin, kidney and liver functions. [61]

The relative bioavailability of repaglinide from its liquisolid compact formula was found to be increased significantly in comparison to that of the marketed tablet. In regard to urea and creatinine, no significant change was recorded after the administration of the commercial and the three potencies of the new formulation compared with the control group. Similarly, in liver function tests (serum glutamic pyruvic transaminase, SGPT), there were no changes observed in its level. Regarding insulin levels, the commercial formula increased insulin levels insignificantly (3.52% change) while the new formula increased the insulin level significantly with a percent change of 37.6%. The results of the glucose tolerance test showed that the blood glucose level was decreased significantly after the commercial drug (percent change, 18.1%) while in groups treated with the new formulation the decrease was highly significant ($p < 0.01$) with a percent change of 29.98%. The change in area under the curve for blood glucose was significantly higher in the commercial drug plus glucose load than in the new formulation plus glucose load group ($p < 0.05$) in the periods of 30-45 min and 45-60 min. In addition, the new RP formulation significantly decreased blood glucose levels more than the commercial formula. [61]

Liquisolid compact of Furosemide (FS) has the capability to increase FS intrinsic solubility. The liquisolid tablets containing Synperonic® PE/L 81 as a novel liquid vehicle shows greater dissolution due to the physical properties of this liquid vehicle, which led to increased wetting properties

and solubility of the drug. PEG 400 as a liquid vehicle failed to improve FS dissolution owing to lower solubility of the drug in PEG 400 compared to Synperonic® PE/L 81 and likely drug-PEG 400 interactions as revealed by DSC and FT-IR data. Since drug dissolution is the rate limiting step in oral drug absorption of non-polar molecules, liquisolid compacts prepared with Synperonic® PE/L 81 might present substantial *in-vivo* dominance over conventional directly compacted counterpart. Caprol® PGE 860 was not a good choice of liquid vehicles to prepare FS liquisolid tablets. There is no single liquid vehicle which is suitable for all poorly water soluble drugs to formulate liquisolid compacts. Therefore, choosing a suitable liquid vehicle, depending on its properties e.g. viscosity, for a particular drug is important to prepare a successful liquisolid tablets. [62]

Carbamazepine (CBZ) is an anticonvulsant drug; the anticonvulsant activity was evaluated in the liquisolid tablets, suspension and the marketed tablets by using the maximal electroshock method. Male albino mice, weighing 20-25mg, were fasted overnight and divided into four groups, each consisting of six animals. CBZ, supplied from the different above products to mice in a dose of 35mg/kg body weight. Maximal electroshock seizure (MES) was induced using an electrical simulator with ear electrodes to deliver stimuli. An electrical stimulus (50mA, 60 Hz) was delivered for 0.2 s to the animal after 60 min of drug administration. The animals were restrained by hand and released at the moment of stimulation in order to permit the observation of the entire seizure. Absence of hind limb tonic extensor component indicated that the drug received could prevent MES spread. The results were expressed as percentage of the animals protected. [52]

Liquisolid Compacts of Aceclofenac orodispersible tablets were formulation and evaluated. The study is based on the effect of combined mixture of super disintegrants disintegrating action on drug release. Propylene glycol, PEG 400, Tween 80, microcrystalline cellulose were used as carrier. The liquisolid compacts with Sodium starch glycolate added intra granularly and Crosspovidone extra granularly showed highest dissolution rate. Orodispersible liquisolid compacts prepared with Tween 80 enhance the dissolution rate of aceclofenac to a larger extent. [63]

Ketotifen fumarate sublingual tablets, was prepared by using the fast-melt granulation technique. The powder mixtures containing the drug were agglomerated using a intermingle of polyethylene glycol 400 and 6000 as meltable hydrophilic binders. Granular mannitol or granular mannitol/sucrose mixture is used as fillers. A mechanical mixer was used to prepare the granules at 40°C. The method involved no water or organic solvents, which are used in conventional granulation, and hence no drying step was included, which saved time. 12 formulations were prepared and characterized among these, three formulations showed the best results and were subjected to an ex vivo permeation study using excised chicken cheek pouches. The prepared formulation F4I possessed the highest permeation coefficient due to the presence of the permeation enhancer (polyethylene glycol) in an amount which allowed maximum drug permeation, and was subjected to a pharmacokinetic study using rabbits as an animal model. The bioavailability of F4I was significantly higher than that of a commercially available dosage form ($p > 0.05$). Therefore, fast-melt granulation allowed for rapid tablet disintegration and an enhanced permeation of the drug through the sublingual mucosa, resulting in increased bio availability. [64]

This technique is a potential alternative for formulation of water-insoluble/soluble drugs. The enhanced rate of drug dissolution from liquisolid tablets is probably due to an increase in wetting properties and surface area of drug particles obtainable for dissolution. Rapid disintegration rates are experimentally compared to conventional tablets. Hence they show improved release rates and greater bioavailability. By this technique, sustained drug delivery systems were also be developed for the water soluble drugs in which hydrophobic non-volatile solvents are used as vehicles Alteration of formulation by use of definite agent's source it control the release of drugs from the liquisolid tablets.

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